EXHIBIT 10

EXPERT REPORT, ANNA LEMBKE, M.D.

March 25, 2019

MDL No. 2804

Relating to Case Nos. 17-OP-45004 and 18-OP-45090

to my work with my patients. Indeed, given the large and increasing role of opioid drugs in addiction, the fields of addiction and pain medicine are inevitably intertwined, such that it is essential to my practice to remain aware of the state of scientific inquiry in both fields. Specifically for this Report, I have considered the materials listed on Exhibit B, attached. I hold the opinions stated in this Report to a reasonable degree of scientific certainty.

22. A statement of my testimony within the last 4 years is attached as Exhibit C and a statement of my compensation rate for consulting work is attached as Exhibit D.

B. Opinions

For the reasons set forth in detail in this Report, I hold the following opinions:

1. Addiction is a chronic, relapsing and remitting disease with a behavioral component, characterized by neuroadaptive brain changes resulting from exposure to addictive drugs. Every human being has the potential to become addicted. Some are more vulnerable than others. Risks for becoming addicted include genetic, developmental, and environmental factors (nature, nurture, and neighborhood). One of the biggest risk factors for addiction is simple access to addictive drugs. Prescription opioids are as addictive as heroin, and the Defendants' conduct in promoting widespread access to prescription opioids has inevitably resulted in an epidemic of opioid addiction.

2. Opioid prescribing began to increase in the 1980's, and became prolific in the 1990's and the early part of the 21st century, creating more access to opioids across the U.S. population, and representing a radical paradigm shift in the treatment of pain. Prior to 1980, doctors prescribed opioid pain relievers sparingly, out of appropriate concern that their patients would get addicted, and then only for short term use in cases of severe injury, surgery, or at the very end of life.

3. The Pharmaceutical Opioid Industry increased sales of prescription opioids, by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like The Joint Commission, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread opioid prescribing.

4. The Pharmaceutical Opioid Industry encouraged and promoted several misconceptions concerning opioid use, including the following:

   a. overstatement of benefits of long-term use for chronic pain. In fact, there is not, and has never been, reliable evidence that long-term opioid use improves pain or function to any clinically meaningful degree. The best evidence available shows that there is little or no improvement in pain or function for most patients on long-term opioid therapy. Patients often endorse ongoing subjective benefit from the opioid, not because it is treating underlying pain, but because it is relieving opioid withdrawal from the previous dose. Studies show that pain improves when patients on chronic high dose opioid therapy reduce their dose or come off opioids.

e. From a neuroscience perspective, addiction is a disorder of the brain's reward circuitry.[14] Opioids, in addition to binding the mu-pain receptors, also cause the release of the neurotransmitter dopamine. In order to accommodate the high amount of dopamine released, the brain adapts by downregulating its own endogenous dopamine and its own endogenous dopamine receptors. This process is called neuroadaptation, and the result is a dopamine deficit state, wherein the threshold for experiencing pleasure goes up, and the threshold for experiencing pain goes down. Addicted individuals then need the substance not to feel good, but to escape the pain of withdrawal.

f. In severe forms of addiction, individuals commit all available resources to obtaining more of the substance, even forgoing natural rewards like food, finding a mate, or raising children.[15] By hijacking the brain's reward and motivational centers, addiction leads to compulsive, self-destructive consumption that overcomes the limits of voluntary choice.

g. Because addiction affects the same neural pathways evolved over millions of years to encourage humans to seek out pleasure and avoid pain, everyone is vulnerable to the disease of addiction. Or as Nora Volkow, Director of the National Institute on Drug Abuse, and Thomas McLellan, former Deputy Director of the Office of National Drug Control Policy, wrote in their review "Opioid Abuse in Chronic Pain" in the New England Journal of Medicine (2016), "no patient is immune to addiction."[16] Without activation by consumption of the drug, the disease of addiction does not exist. This is supported by studies that have identified a dopamine receptor deficit state among those exposed to addictive drugs, compared to healthy subjects who have not been exposed.[17] Exposure to/consumption of the addictive substance is a necessary criterion for the development of addiction to that substance.

2. Opioid prescribing began to increase in the 1980's, and became prolific in the 1990's and the early part of the 21st century, creating more access to opioids across the U.S. population, and representing a radical paradigm shift in the treatment of pain. Prior to 1980, doctors prescribed opioid pain relievers sparingly, out of appropriate concern that their patients would get addicted, and then only for short term use in cases of severe injury, surgery, or at the very end of life.

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[14] Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010;35:217-238. doi:10.1038/npp.2010.4

[15] Schultz W. Potential vulnerabilities of neuronal reward, risk, and decision mechanisms to addictive drugs. *Neuron*. 2011;69(4):603-617. doi:10.1016/j.neuron.2011.02.014

[16] Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain - Misconceptions and Mitigation Strategies. *N Engl J Med*. 2016;374(13):1253-1263. doi:10.1056/NEJMra1507771, at p. 1254.

[17] Koob *et.al,* "Neurocircuitry," fn. 14, above, p. 223; Volkow ND, Fowler JS, Wang G-J, Swanson JM. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol Psychiatry*. 2004;9(6):557-569. doi:10.1038/sj.mp.4001507 at p. 557

a. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of severe injury or illness, during surgery, or at the very end of life. [18] Doctors' reluctance to prescribe opioids stemmed from the legitimate concern that patients would get addicted.

i. Awareness of the risks of addiction caused by opioids ingested in the context of medical care, dated back at least to the Civil War, when injured soldiers became addicted to morphine, and heroin was available over the counter next to Bayer aspirin as a cough and cold remedy, leading to the opioid epidemic of the early 1900s. [19](

ii. A study published in 1954 reported that 27% of opioid addicted white males (137/508) and 1.2% of African American males (4/330) yielding a combined rate of 16.8% (141/838), became addicted after being treated with opioids for pain. The authors successfully tapered these patients off of opioids, with improved pain and function in more than 80%. The authors concluded, "Morphine is not the answer to chronic pain. Because of the development of tolerance to the analgesic effects of morphine, alleviation of pain becomes inadequate. Under such circumstances the physician, by gradually withdrawing narcotics, does not deprive the patient of any actual benefit but protects him and his family from the possible legal, social, or economic difficulties attendant on opiate addiction. The administration of morphine to a patient with chronic pain is a short-lived type of kindness. Long-term kindness would begin when opiates are withheld or withdrawn in favor of other therapeutic measures."[20]

iii. This history contributed to the longstanding reluctance of the medical profession to prescribe opioids prior to the marketing campaigns carried out by the Defendants as described below.

b. Opioid prescribing tripled between the 1990's and 2012, and dramatically increased in dose and duration. "By 2010, enough OPR [opioid pain relievers] were sold to medicate every American adult with a typical dose of 5 mg of hydrocodone every 4 hours for 1 month." [21]

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[18] Meldrum ML. *Opioids and Pain Relief: A Historical Perspective (Progress in Pain Research and Management, V. 25)*. IASP Press; 2003, at pp. 195-199.
[19] Courtwright DT. *Dark Paradise: A History of Opiate Addiction in America*. Harvard University Press; 2001, at pp. 45-46; 89-91.
[20] Rayport M. Experience in the Management of Patients Medically Addicted to Narcotics. *JAMA - J Am Med Assoc*. 1954;156(7):684-691, at p. 690.
[21] Paulozzi LJ, Jones CM, Mack K a, Rudd R a. Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- {United States}, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm?s_cid=mm6043a4_w, at p. 1489.

prescription was continued (30.5%) than those in which an opioid was newly prescribed (22.7%).[26]

v. As reported in an article I co-authored in 2016, more than one-third of Part D Medicare enrollees fill at least one opioid prescription in any given year. Part D covers 68% of the roughly 55 million people on Medicare.[27] As such, more than 10 million Part D Medicare enrollees are exposed to a prescription opioid in any given year, thus becoming vulnerable to the adverse effects of opioids, including but not limited to addiction. Medicare represents just one patient population, suggesting that many millions of patient consumers in this country have been exposed to the risks of prescription opioids in recent decades, both within and outside the Medicare-eligible populations. As discussed later in this report, much of that exposure resulted from aggressive marketing that overstated benefits and downplayed risks of chronic exposure to prescription opioids.

c. As reported in another article I co-authored in 2016, increased opioid prescribing is distributed across different types of prescribers, relatively indifferent to individual physicians, specialty or region.[28] In other words, opioid overprescribing is not the result of a small subset of so-called 'pill mill' doctors, although such doctors do exist, but rather has been driven by a wholesale shift in medical practice. All doctors across diverse medical specialties are prescribing more opioids.

i. By specialty, pain doctors prescribe more opioids than doctors in any other specialties. However, by volume, family medicine and internal medicine doctors account for the most opioids, simply because there are more of them.[29]

ii. But the salient finding was that opioid prescribing is not driven by a minority of prolific prescribers.[30]

d. Although national average opioid prescribing has plateaued or decreased since its peak in 2012, there are still many cities, counties, and states across the nation where opioid prescribing continues to be high, and overall opioid prescribing in the US remains at levels far exceeding pre-1990 rates.

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[26] Sherry TB, Sabety A, Maestas N. Documented Pain Diagnoses in Adults Prescribed Opioids: Results From the National Ambulatory Medical Care Survey, 2006–2015. *Ann Intern Med*. 2018;169(12):892-894, at p. 892.
[27] Lembke *et al.*, "Use of Opioid Agonist Therapy", fn. 5, above, at pp. 990-991.
[28] Chen et.al, "Distribution of Opioids", fn 4, above, at p. E2.
[29] *Id.* at pp. E1-E2.
[30] *Id.* at p. E2.

iv. I have personally experienced this CME strategy. For example, in 2001, every licensed physician in the state of California was mandated to attend a day-long CME course on the treatment of pain as a requirement to maintain licensure. I attended that day-long course, in which use of opioids was promoted. I recall that there was no accurate presentation of the risks of opioids, and the messages that were provided tracked the misconceptions described above regarding overstatement of the benefits of opioids.

v. Consistent with and supportive of my personal experience, Dr. Joel Saper, a past board member of the American Pain Society (APS), testified that "the educational programs of AAPM [American Academy of Pain Management] and APS particularly as they involve opioid advocacy, were greatly influenced by commercial largess. In my opinion, commercial dynamics influenced, if not steered, the selection of abstracts, course topics, and faculty to commercially friendly participants as it involved opioid advocacy, largely ignoring those imposing or exhorting caution against the growing advocacy for opioids for chronic nonmalignant pain.[49] Dr. Saper testified that such educational programs of AAPM and APS involving opioid advocacy were "inappropriate"[50] , and I agree.

vi. Dr. Saper further stated that "APS and AAPM and its members have participated, if not promoted, this crisis by failing to assure the presentation of unbiased, balanced educational programs and guideline development, thereby protecting the public from commercial influence through undisclosed support from the opioid industry. In failing to do so, the organizations failed to protect patients."[51]

vii. Further, an internal Purdue Pharma email from Richard Sackler to Paul Goldenheim, dated April 13, 2001, concerned a planned meeting with "leaders of APS, APF [American Pain Foundation] and other pain societies." Dr. Sackler stated, "Our goal is to bind these organizations more closely to us than heretofore, but also to align them with our expanded mission and to see that the fate of our product(s) are [sic] inextricably bound up with the trajectory of the pain movement."[52]

viii. The use of "Speakers Bureaus" of doctors, trained by a drug company to promote its product, is an adjunct to the CME strategy.

[49] Deposition of Joel R. Saper, M.D., January 11, 2019, MDL No. 2804, at 92:13-22.
[50] *Id.* at 93:15-19.
[51] *Id.* at 115:24-116:6
[52] PPLPC045000004928- PPLPC045000004933 at 4929.

risk associated with opioids themselves, has been the prevailing thinking in the 1980's, 1990's, and 2000's, encouraged by the Defendants' promotional messages, and is in part responsible for the opioid epidemic we face today. Prescribers were incorrectly taught that by screening out high risk patients, they would avoid opioid misuse and addiction.

g. Further, because of Defendants' aggressive promotion of the great benefits and minimal risks of prescribing opioids for pain, it would have been reasonable for doctors to conclude that there was little or no need for screening.

h. Finally, it is unlikely that asking patients about risk factors will ever be a suitable method of screening, as motivation to minimize or omit risk factors in pursuit of obtaining a specific type of drug will weigh heavily on the truthfulness and transparency of reporting (See discussion of Fleming study, above).

10. In sum, the Pharmaceutical Opioid Industry made misleading marketing claims to promote the above misconceptions, in the absence of reliable scientific evidence. Taken together, these misconceptions were the single most significant factor giving rise to the massive increase in the sale of opioids and the resulting epidemic of dependence and addiction, as detailed in this Report. Further, the actions of the Pharmaceutical Opioid Industry significantly influenced doctors and others who made decisions that increased the population's exposure to prescription opioids. Other developed countries with similar populations that experience chronic pain, but which have not had the same aggressive marketing as in the U.S., have not experienced any comparable degrees of prescription opioid overuse, mortality, and morbidity, supporting the conclusion that the marketing is the factor that made the difference.

a. To understand how insidious, pervasive, and misleading the opioid marketing was (and continues to be to this day), it is relevant to examine a published peer reviewed article in the medical literature on pain and opioids, dissect the misleading science contained therein, trace the affiliation of its authors back to opioid manufacturers, and uncover how a 'scientific article' was then used by opioid manufacturers as promotional material. In other words, peer reviewed articles written by key opinion leaders and/or sponsored by the Defendants, were disseminated to prescribers under the guise of science, when in fact they represented marketing tools. To illustrate, an example is provided below.

i. A report by Endo Pharmaceuticals created for its sales representatives included reference to an article by Katz et al, "A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid naive

e. As I wrote in my book, Drug Dealer, M.D.,[318] doctors were "duped" by the Pharmaceutical Opioid Industry into believing the myths of substantial benefits and very low risks of prescription opioids. I also wrote in my book that others had some responsibility for the events that have transpired. The roles of other parties are summarized below. In addition, on the basis of my review of documents that were provided to me in this case, I am more aware of the Pharmaceutical Opioid Industry's role in influencing some of those other parties to act in the way they did.

i. The Federation of State Medical Boards (FSMB) is a national organization that oversees the 70 medical and osteopathic boards of the United States and its territories. The State Board organizations serve many functions, but the most important is to police doctors, and exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor's license to practice medicine.

A. In 1998, the Federation of State Medical Boards released a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. Further, the Federation urged state medical boards to punish doctors for under-treating pain. Doctors lived in fear of disciplinary action from the State Medical Boards, and the lawsuit that usually followed, if they denied a patient opioid painkillers. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to adopt its Model Policy to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct.

B. In 2001, every licensed physician in the state of California was mandated to attend a day-long course on the treatment of pain, as a requirement to maintain licensure. I attended one of these courses, and to my recollection, all of the false messages promoted by the Defendants were highlighted in this CME course, including overstatement of benefits, and understatement of risks.

C. The Federation of State Medical Boards published a book promoting the use of opioid painkillers. This book was sponsored by a "consortium" that included Abbott

[318] Lembke, "*Drug Dealer, MD,*" fn. 2, above.

Laboratories, Alpharma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, the Wisconsin PPSG, and Purdue Pharma[319]. (See Appendix II).

D. As detailed in Appendix II to this Report, the Pharmaceutical Opioid Industry provided substantial funding to the Wisconsin PPSG, which lobbied State Medical Boards to increase access to opioids, preclude punishment if opioids were prescribed for pain, and classify undertreatment of pain as inappropriate conduct. PPSG played a central role in revising the Federation of State Medical Board's Model Guidelines on the Use of Controlled Substances for Pain Management[320], now entitled Model Policy for the Use of Controlled Substances for Pain Management.[321]

ii. The Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. They are responsible for approving drugs before they reach the market, and monitoring the safety and marketing of those drugs after they are publicly available. In my book, Drug Dealer, MD, I assigned some responsibility for the prescription drug epidemic to the FDA, and to the Defendants for efforts to influence the FDA. However, it is my understanding that other witnesses with expertise on FDA-related matters will offer testimony on such issues at trial, and, accordingly, I do not intend to testify on issues relating to the FDA.[322]

iii. The Toyota-ization of Medicine

A. The majority of doctors today work in large integrated health care systems. During the 1990's and 2000's, there occurred a mass migration of doctors out of private practice and into managed care organizations. In 2002, 70% of U.S. physician practices were physician-owned. By 2008, more than 50% of U.S. physician practices were owned and

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[319] Fishman, S.(ed.), "Responsible Opioid Prescribing: A Physician's Guide" (Federation of State Medical Boards, Waterford Life Sciences, 2007).
[320] WIS_PPSG_008292, 11/30/2005
[321] http://www.fsmb.org/Policy%20Documents%20and%20White%20Papers/2004_model_pain_policy.asp
[322] Lembke, "*Drug Dealer, MD,"* fn. 2, above; Fauber J. FDA and Pharma: Emails Raise Pay-for-Play Concerns. *Sentinal/MedPage Today*. October 7, 2003, see http://www.medpagetoday.com/PainManagement/PainManagement/42103,at p. 1.

(65.5%), Indiana (35.1%), Ohio (27.7%), and Missouri (21.4%)."[336]

iv. Unlike the available fatal overdose data, which are categorized according to non-fentanyl prescription opioids, heroin, etc., the CDC/ESOOS on emergency department visits are not broken out into categories. Although the cumulative total of prescription opioid mortality since 1999 exceeds mortality for fentanyl plus heroin, the mortality rate for the latter category has recently begun to exceed the former; it is likely that the nonfatal overdose hospital admissions have occurred in a similar ratio of prescription opioids to illicit heroin and fentanyl.

v. As described previously, tens of thousands of Americans experience non-fatal overdose, both in medical settings, like the emergency department, and in the field, creating a significant burden on the health care system and on first responders, not to mention the victims of near overdose themselves. In a paper by Dunn et al,[337] previously discussed, the over 14,000 fatal prescription opioid overdoses in 2017[338] would translate to over 100,000 nonfatal overdoses during that same year. While fatal cases justifiably capture our attention, it must also be recognized that the cost of a nonfatal overdose is far greater in terms of medical and community resources, to treat the overdose episode itself, and to provide long-term care for the OUD disease that gave rise to the event.

12. We are now in the second and third waves of this epidemic, with a spike in deaths from illicit opioids, particularly heroin (second wave) and illicit fentanyl (third wave). There is a clear link between prescription opioid exposure and the subsequent use of heroin and other illicit opioids. The likelihood of heroin addiction is 40 times greater in those who have previously misused or been addicted to prescription opioids, and fentanyl, in turn, has contaminated the heroin supply.

a. "A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use[339]… The interrelated nature of the

[336] Vivolo-Kantor AM, Seth P, Gladden RM, Mattson CL, Baldwin GT. Vital Signs : Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States , July 2016 – September 2017. 2018;67(9):279-285, at p. 281.
[337] Dunn, *et al.*, "Opioid Prescriptions," fn. 268, above.
[338] CDC, Data Brief 329, fn 327, above, at p. 4.
[339] National Academies of Science Engineering and Medicine (NASEM), "Pain Management and Opioid Epidemic 2017," fn. 133, above, at p. 215.

18. With an aggressive infusion of resources and efforts in these two counties, it would be reasonable that within four years the percentage of bellwether individuals with OUD who receive MAT could quadruple from approximately 7% of individuals with OUD currently to approximately 28% of individuals with OUD. Note: 7% estimate based on assumption that 1/3 of individuals receiving treatment also receive MAT. Corresponds to national figures that less than 10%with OUD receive MAT.[378]

a. Once the populations receiving treatment/MAT are increased as described above, it would be necessary to provide treatment at those same levels for the foreseeable life expectancy of the patients, because OUD is a disease with constant risk and high rate of relapse and remission.

b. If the treatment rates described above are achieved, there would be a large impact on deaths and other outcomes, as evidenced by the experience in Massachusetts and Vermont, described above. The mix of MAT that is buprenorphine and naltrexone-based will continue to increase relative to methadone-based

D. Conclusion:

The ongoing epidemic of morbidity and mortality due to prescription opioids is the result of aggressive marketing and promotion of such drugs, and in particular the overstatement of benefits and understatement of harms. Opioid manufacturers engineered the increase in opioid prescribing by directly targeting doctors, by promoting key opinion leaders, by infiltrating continuing medical education courses, by supporting professional medical societies, and by co-opting medical watchdog organizations like *The Joint Commission*, to convince prescribers that liberal opioid prescribing is based on science. In fact there has never been sufficient evidence to justify widespread use.

Authoritative reviews have concluded that the evidence of benefits for chronic pain is "weak," "inconclusive," and "insufficient to assess effects on health outcomes." Defendants' clinical trials were too short to provide reliable evidence of long-term benefit, especially in light of highly selected populations and substantial rates of attrition from the studies. As shown by the SPACE trial, a gold standard, long-term study by independent researchers, non-opioids are as good or better than opioids for chronic pain, and have fewer side effects. On the risk side, Defendants claimed that addiction was "rare," "uncommon," or "less than 1%," based on inapplicable data from non-comparable populations. The true rate of addiction in a clinical population is probably closer to 21-29%, across the full spectrum of OUD. In addition, there are millions of patients today who are physiologically dependent on opioids, unable to reduce their doses, and left to suffer the risks and consequences of long-term opioid therapy.

Ending the epidemic of opioid addiction, dependence, and death will require significant investment of resources. An effective strategy will be multifaceted, and will accomplish the

[378] Sandoe, E., *et al.*, "Policy Levers That States Can Use to Improve Opioid Addiction Treatment And Address the Opioid Epidemic", Health Affairs Blog. (Oct. 2, 2018). See https://www.healthaffairs.org/do/10.1377/hblog20180927.51221/full/

following: prevent new cases of addiction, dependence, and other related harms (primary prevention), limit progression of harm (secondary prevention), and treat existing cases (treatment). In a *New England Journal of Medicine* commentary regarding the CDC Opioid-Prescribing Guideline, CDC physicians Thomas Frieden and Debra Houry stated, "We know of no other medication routinely used for a nonfatal condition that kills patients so frequently."[379]

Dated: March 25, 2019

Anna Lembke, M.D.

[379] Frieden TR, Houry D. Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline. *N Engl J Med*. 2016. doi:10.1056/nejmp1515917, at p. 1503.